Distribution of the Matsuda Index in Japanese healthy subjects

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ABSTRACT

We investigated the cut-off point of the Matsuda Index in Japanese according to the guideline from the Clinical and Laboratory Standards Institute. A total of 1,596 subjects free from medications for diabetes mellitus, dyslipidemia and/or hypertension, and without cardiovascular diseases or chronic renal failure underwent a health check-up and oral glucose tolerance test (OGTT). We recruited 204 healthy reference individuals with normal glucose tolerance without obesity, any component of metabolic syndrome or elevated alanine aminotransferase. The Matsuda Index was calculated with 0- and 120-min data during OGTT. As the index was not normally distributed (P < 0.001 by the Shapiro–Wilk test), the log-transformed value (P = 0.876 by the Shapiro–Wilk test) was used. The mean ± 2 standard deviations were taken as the reference limits. The lower reference limit of the Matsuda Index was then calculated to be 4.3. Our result shows that a Matsuda Index <4.3 indicates the presence of insulin resistance in Japanese. (J Diabetes Invest, doi: 10.1111/jdi.12056, 2013)

KEY WORDS: Insulin resistance, Matsuda Index, Reference limit

INTRODUCTION

Insulin resistance plays important roles in the pathogenesis of diabetes mellitus[1], as well as metabolic syndrome[2]. It is usually assessed by some indices, such as the homeostasis model assessment of insulin resistance (HOMA-IR)[3] and insulin sensitivity index proposed by Matsuda and DeFronzo (Matsuda Index)[4,5]. Elevated values of HOMA-IR and reduced values of the Matsuda Index indicate the presence of insulin resistance, although little was known about their valid cut-off points in Japanese subjects. A recent report successfully showed that HOMA-IR ≥2.5 was a reasonable cut-off point in Japanese[6]. They drew this reference limit based on the C28-A3 document by the Clinical and Laboratory Standards Institute (CLSI)[7].

In contrast, the optimal cut-off point of the Matsuda Index in Japanese has not been clearly established. We therefore investigated the optimal reference limit of the Matsuda Index in a Japanese population, in accordance with the CLSI guideline[7].

METHODS

We used cross-sectional data in the Amagasaki Visceral Fat Study (UMIN000002391). The study was approved by the human ethics committee of Osaka University, and written informed consent was obtained from every participant. A total of 1,596 Japanese employees of Amagasaki City Office who were free from current treatment of diabetes mellitus, dyslipidemia and/or hypertension, and had no history of cardiovascular diseases or chronic renal failure, underwent a health check-up and 75-g oral glucose tolerance test (OGTT). Of these participants, 204 had normal glucose tolerance without obesity (i.e., body mass index ≥25 kg/m^2), any component of metabolic syndrome[2] or elevated alanine aminotransferase (≥31 IU/L)[6]. We used these participants as the healthy reference individuals. Normal glucose tolerance was diagnosed when fasting plasma glucose levels were <6.1 mmol/L and 2-h plasma glucose levels were <7.8 mmol/L under 75-g OGTT[1].

The Matsuda Index was calculated from 0- and 120-min data during 75-g OGTT[4]. We investigated its reference limits according to the CLSI guideline[7], using parametric estimation. The normality of the distribution was assessed by the Shapiro–Wilk test, and the transformation to fit a Gaussian distribution was carried out when necessary. The obtained lower reference limit of the Matsuda Index was regarded as the cut-off point for detecting insulin resistance. As 30- and 60-min data during OGTT were also available, we additionally calculated Matsuda indices from 0-, 30-, 60- and 120-min data, and that derived from 0-, 60- and 120-min data[4], and showed their individual cut-off points. Mean plasma glucose and insulin concentrations during OGTT were estimated by the trapezoid method. Furthermore, to validate the adequacy of the current reference population, we also assessed HOMA-IR[3] and investigated whether the obtained optimal cut-off point was comparable to 2.5, the recommended cut-off point by the Japan Diabetes Society[1]. Data are given as means and standard deviations (SD). Statistical analyses were carried out using IBM SPSS Statistics Version 19 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the clinical characteristics of the reference population. Their age ranged from 23 to 69 years. The Matsuda

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Table 1 | Baseline characteristics of the study population

No. recruited patients (male:female)	204 (144:60)
Age (years)	49 ± 9
Body mass index (kg/m^2)	21.5 ± 1.8
Waist circumference (cm)	76 ± 5
Fasting plasma glucose (mmol/L)	5.1 ± 0.4
2-h plasma glucose (mmol/L)	5.5 ± 1.2
Systolic blood pressure (mmHg)	114 ± 9
Diastolic blood pressure (mmHg)	70 ± 8
Triglycerides (mmol/L)	0.9 ± 0.3
HDL cholesterol (mmol/L)	1.8 ± 0.4
Alanine aminotransferase (IU/L)	16 ± 5

Data are mean ± standard deviation. HDL, high-density lipoprotein.

Index and HOMA-IR were significantly correlated with each other (ρ = –0.79; $P < 0.001$). The Shapiro–Wilk test denied the normality of the Matsuda Index ($P < 0.001$); its distribution showed a right-skewed shift from the Gaussian distribution (Figure 1a). The variable was therefore log-transformed to fit the Gaussian distribution ($P = 0.876$ by the Shapiro-Wilk test), as shown in Figure 1b. The log-transformed Matsuda Index (Ln Matsuda Index) was distributed as 2.71 ± 0.63. We affirmed that the population had no outliers defined as 3 SD lower or higher than the mean value. The lower reference limit of Ln Matsuda Index, or mean – 2SD, was calculated to be 1.45. The reference limit corresponded to 4.3 of the Matsuda Index, indicating that a Matsuda Index <4.3 represents the presence of insulin resistance.

When Matsuda indices were calculated from 0-, 60- and 120-min data, and from 0-, 30-, 60- and 120-min data, their log-transformed values were distributed as 2.62 ± 0.57 and 2.50 ± 0.53, respectively. The lower reference limits of the indices were therefore calculated to be 4.4 and 4.2, respectively.

We subsequently investigated the cut-off point of HOMA-IR. The Shapiro–Wilk test denied the normality of HOMA-IR (P <0.001), but not of log-transformed HOMA-IR ($P = 0.587$). We therefore estimated the reference limit of the variable after log-transformation. Consequently, the upper reference limit of HOMA-IR was calculated to be 2.4, indicating that HOMA-IR ≥2.5 represents insulin resistance, as previously shown.

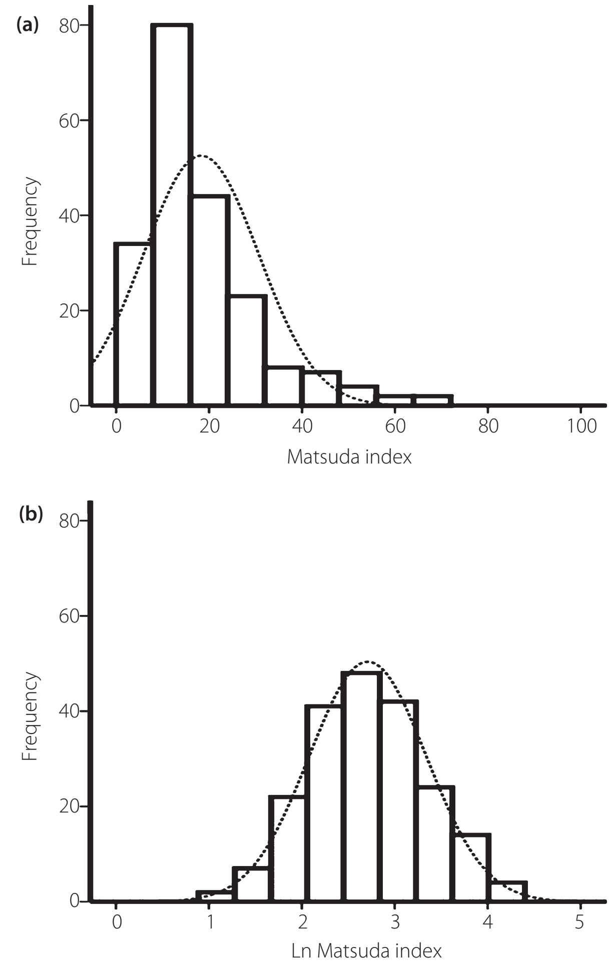

Figure 1 | Histograms of (a) the Matsuda Index and (b) its log-transformed (Ln) value.

DISCUSSION

We investigated the optimal cut-off point of the Matsuda Index in Japanese, according to the CLSI guideline[7], using the data of 204 healthy participants. The sample size was large enough to meet the recommendation (≥120). As discussed in the guideline, "Health is a relative condition lacking a universal definition. Defining what is considered healthy becomes the initial problem in any study." We selected "healthy" reference individuals from those without mediation for hypertension, dyslipidemia and/or diabetes mellitus, and without cardiovascular disease or chronic renal failure, similarly to the previous report of HOMA-IR[6]. The previous study finally defined healthy reference individuals as those with normal glucose levels without obesity or elevated alanine aminotransferase. In contrast, we defined them more strictly. In addition to these criteria, we excluded those with any component of metabolic syndrome, because the components were well known to be associated with insulin resistance[2]. We also detected normal glucose tolerance by OGTT. The adequacy of the current definition of "healthy" subjects would be validated partly by the findings that the HOMA-IR cut-off point derived in the current study was equivalent to that recommended by the Japan Diabetes Society[1].

One study carried out in the USA[8] treated a Matsuda Index ≤2.5 as insulin resistance, because that was the lowest tertile of the studied population with normal glucose tolerance, most of whom were Hispanic. Their cut-off point was lower than ours. One explanation for this discrepancy might be the different analytic procedures. As aforementioned, the current study obtained the cut-off point according to the CLSI guideline. Furthermore, we calculated the Matsuda Index using 0- and

120-min data during OGTT[5], whereas they calculated the index from the 0-, 30-, 60-, 90- and 120-min data, according to the original report[4].

Another reason for the different cut-off points could be ethnic difference. It has been pointed out that different ethnic populations have different body composition[9–11]. It is possible that these differences yield the different distribution of insulin sensitivity indices. Indeed, the proposed cut-off points of HOMA-IR were different between Asian and non-Asian populations[1,6,12–15]. It would be no surprise if ethnic difference gives different cut-off points of the Matsuda Index.

The current study had some limitations. First, we did not analyze the data of a morbid population who were confidently expected to have insulin resistance. The distribution of their Matsuda Index remains unknown. However, the current analytical procedures were in accordance with the CLSI guideline, and we believe the validity of the current investigation. Second, we did not assess insulin sensitivity by euglycemic hyperinsulinemic clamp. Instead, we excluded in the current study all the participants who were clinically expected to have insulin resistance. Future studies using euglycemic hyperinsulinemic clamp will be required to validate the reference limit drawn in the current study.

In conclusion, the current study investigated the optimal cut-off point of the Matsuda Index, according to the CLSI guideline, using the data of the healthy reference population. A Matsuda Index <4.3 could be proposed as the optimal cut-off point showing the presence of insulin resistance in a Japanese population.

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